MOLECULAR DYNAMICS SIMULATION OF IBUPROFEN CRYSTAL POLYMORPH

MOHAMMAD SAFUAN BIN MAT NOOR

Thesis submitted in partial
fulfillment of the requirements for the award of the
degree of Bachelor of Chemical Engineering

Faculty of Chemical and Natural Resources Engineering
UNIVERSITI MALAYSIA PAHANG

FEBRUARY 2012

MOLECULAR DYNAMICS SIMULATION OF IBUPROFEN CRYSTAL POLYMORPH

ABSTRACT

Ibuprofen (iso-butyl-propanolic acid) is one of the Active Pharmaceutical Ingredients (API) that uses to treat a symptom of rheumatism, arthritis, fever, as an analgesic (pain reliever). This study aims to identify which solvents should affect the polymorph of ibuprofen begins from the crystallization solution. The Molecular Dynamics Simulation and Fourier transform infrared (FTIR) is used to recognize which molecules that form hydrogen bond in the ibuprofen crystal polymorph. The study analysis has shown that the higher hydrogen bond between the atoms will contribute to the ibuprofen crystal polymorph. As the conclusion, only the selected atoms will contribute in the formation of desired crystal polymorph of ibuprofen.

Keywords : radial distribution function, diffusion coefficient, hydrogen bonding

SIMULASI DINAMIK MOLEKUL IBUPROFEN KRISTAL POLIMORF

ABSTRAK

Ibuprofen (iso-butil-propanolic asid) adalah salah satu daripada Ramuan Aktif Farmaseutikal (API) yang digunakan untuk merawat gejala penyakit reumatisme, artritis, demam, sebagai analgesik (pelega kesakitan). Kajian ini bertujuan untuk mengenal pasti pelarut mana akan menjejaskan polimorf ibuprofen bermula dari larutan kristal. Simulasi Dinamik Molekul dan Jelmaan Fourier Inframerah (FTIR) digunakan untuk mengiktirafkan molekul yang membentuk ikatan hidrogen di ibuprofen Kristal polimorf. Analisis kajian telah menunjukkan bahawa hidrogen yang lebih tinggi ikatan antara atom akan menyumbang kepada ibuprofen kristal polimorf. Sebagai kesimpulan, hanya atom yang dipilih akan menyumbang dalam pembentukan diingini kristal polimorf ibuprofen.

Katakunci: fungsi agihan jejarian, pekali resapan, ikatan hidrogen

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

t	Time
D	Diffusion coefficient
Å	angstrong
C	Concentration
r	Radius
ρ	Density
N	Number of molecules
r	radial
ps	pico second
ns	nano second
g (r)	Radial distribution function

LIST OF ABBREVIATIONS

DHB	Dihydroxybenzoic Acid
COMPASS	Condensed-phase optimized molecular potential for atomistic simulation studies
NVE	Microcanonical Ensemble
NPT	Isobaric-Isothermal Ensemble
RDF	Radial distribution function
MSD	Mean square displacement
OPLS	Optimized Potentials for Liquid Simulations

CHAPTER 1

INTRODUCTION

In this chapter, its cover why the ibuprofen is used as the main element in the active pharmaceutical ingredients for the research. In this chapter also cover what are the problems in the pharmaceutical industry and to be specified the problem in the crystallization of ibuprofen polymorph. Besides that, the chapter will cover all the objectives in this study and what are the significances of this study toward our future development in the pharmaceutical sector.

1.1 Background of Study

Ibuprofen is one of the famous active pharmaceutical ingredients (API) in the current pharmacy industry. Ibuprofen or iso-butyl-propanoic phenolic acid is of being a

well known drug that used to treat a symptom of rheumatism, arthritis, fever, as an analgesic (pain reliever), especially where there is an inflammatory component and dysmenorrhea. It is also applicable to use for pericarditis and patent ductus arteriosus (Derksen, 1995). Ibuprofen is a common non-steroidal anti-inflammatory drug (NSAID). NSAID can be described as the drugs with analgesic and antipyretic (fever reducing) effects and which have higher dose anti-inflammatory effects. Besides that, the ibuprofen is known to have an effect of antiplatelet, though it is relatively mild and somewhat short-lived if compare with others API such as aspirin and others better known antiplatelet drugs. Aspirin breaks down in the solution which completely different with the ibuprofen. Ibuprofen in which state is stable and that makes the ibuprofen available in the topical gel form thus can be absorbed by the skin, and can be used for the sports injuries that theoretically have the least risk of digestion problem. Besides this properties of the ibuprofen, ibuprofen is classified as an important part or core in the medicine of the World Health Organization's" WHO Model List of Essential Medicines", which is a list of minimum medical needs for basic health care system (Kouimtzi, 2009).

1.2 Problem Statement

Polymorphism and solvate formation represents a major issue in pharmaceutical crystallization to the pharmaceutical industry and in terms of patent establishment and protection, reliability of production, and stability on storage and in processing. So, it is very compulsory to study the method in order to solve the problem in the pharmaceutical crystallization. Different types of solvent used will affect the interaction between the

solute-solvent and how do solute-solvent interactions to reflect the polymorphism due to the different solubility. The chosen of solvent also will be considered in this research for the ibuprofen crystal polymorph.

1.3 Research Objectives

This study aims to identify which solvent should affect the polymorph of ibuprofen begin with the crystallization solution and to investigate the correlation between the intermolecular forces of the molecules by the radial distribution function and hydrogen bond existing in the structure.

1.4 Research Questions/Hypothesis

The research question in this study is to identify which solvent will affect the polymorph of ibuprofen by the crystallization solution and to relate between inter-atomic distances between specified atoms in solute molecules that is ibuprofen.

1.5 Scope of Study

The study covers the research by the molecular dynamics simulation and by the experimental analysis. The molecular dynamics simulation consists of 2 systems which pure and binary system at 298.15K. It is will include the system for ethanol and ethyl

acetate. For the experimental analysis, the study will cover by the molecular recognition by using the Fourier transform infrared (FTIR) for the ethanol, hexane and ethyl acetate at saturated solution at 298.15K.

1.6 Expected Outcome

The expected outcome of this study is to clearly understand on how the solute-solvent interaction influences the crystallization by the analysis through the experimental study and also through a simulation study. Another outcome predicted is how the different solvent used affects the solubility of an ibuprofen by study of experiment and by the simulation.

1.7 Significance of Study

There are 4 significance of this study which towards our medical, engineering, economics and environment. For the medical aspects, the efficiency of the drug depends on its solubility which strongly influence by the choice of crystal structure used in processing the drug. For the second aspect which the engineering aspect, this study will able fully understand the correlations in the inter-atomic distances between specified atoms in solute molecules by determine the of Radial Distribution Function (RDF). And in the economic aspect, by using the molecular dynamic simulation all the new therapies and to develop the existing one can only be done by using the molecular dynamic simulation since the price for the active pharmaceutical ingredients is expensive.

Meanwhile, in the environmental aspect, the simulation will prevent the dispose of hazardous waste to the environment.

1.8 Conclusion

At the conclusion, in this chapter able to identify why this study has been proposed and what is the problem with this study. All the scope of study must fully cover in order to achieve our objective in this study and what will it's done towards our future in terms of medical, engineering, economics and environment.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter is the review of previous research on the related topic with this study and by this literature review, helps fully understand that study that had been done and also the problem that current researcher try to solve for the benefit of the human kind and also all the living things in the earth. One of the objectives of this chapter is to understand the full concept and ideas about the ibuprofen, crystallization, active pharmaceutical ingredients (APIs), dynamic simulation and also all the aspects related to the topic of research. It will explain the application of the ibuprofen in the current pharmacy industry and also the important aspect that need to be considered in the producing the crystal

ibuprofen. Besides that, it will also explain about the polymorphism also for the ibuprofen.

The literature review is done based on the journals that are related ibuprofen crystal polymorph and also the dynamic simulation of it. The literature review will cover the characteristic of ibuprofen. This chapter will also cover the active pharmaceutical ingredients (APIs). The software used in the simulation also will be considered to gain the most accurate result for the simulation of the compound. This chapter will let the reader know the importance of ibuprofen. The concept of crystallization method used in obtains the crystal structure of ibuprofen.

2.2 Crystallization

Crystal that obtains from the solution by the process called crystallization, Crystallization is a procedure used in the chemical industries for the preparation of the many types of solid (e.g. pharmaceutical products, chemical intermediates, specialty chemicals, catalyst) (Micheal et al. 2008) and it's widely used for the purification of drugs during the final stages of the process under the pharmaceutical products industries (Garekani and Sadeghi, 2001). Many drugs exist in the crystalline solid form because of the stability and ease handling during the various stages of the process and development. Crystalline solid can appear in the form of polymorph, solvates or hydrates (Jacob et al. 2011). Several key properties of the resultant materials originate from this process,

including chemical purity and composition, internal structure (polymorph state), size and shape distribution and detect density (crystallinity).

It is very significant to control the crystal form of the drug during the different stages of process because any phase changes due to the polymorph interconversions, desolvation of solvates, formation of hydrates and changes in the degree of crystallinity can alter the bioavailability of the drug. The solid drug may experience a change in the thermodynamic properties during the phase transition, with consequent changes in the transport characteristics and its dissolution (Vippagunta et al. 2001). The solvent use will have a larger impact on the resulting morphology by the process crystallization but the consistent prediction not yet can be determined (Horst et al. 2001). Even the chemical composition of the crystalline polymorph is the same but it gives different in the internal crystal structures and therefore, posses' different physic-chemical properties (Borka and Haleblian, 1990).

Few models exist for predicting the morphology of crystal grown from solution. The solvent - crystal interface of the molecular level simulation have been successfully used to predict the shapes of several organic crystal systems. This method makes us use of pure solvent properties and does not require molecular level fluid-phase simulations for designing solvents for crystallization process that related to the hydrogen bonding solubility parameter of solvent and crystal morphology that resulting the desire crystal polymorph (Acquah et al. 2008). And for this study, the researcher has already highlighted the solvent as the parameters in the crystallization process since they solvents play a significant role in the crystalline of the solid.

2.1.1 Crystallization of Active Pharmaceutical Ingredients (APIs)

Active pharmaceutical ingredients (APIs) are defined as the any substance or combination of substances used in a finished pharmaceutical product, intended to furnish pharmacological activity or otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to have a direct effect in restoring, correcting or modifying physiological functions in- human beings . It is frequently delivered to the patient in the solid-state as part of the approved dosage form (e.g. tablets, capsules, etc..) and each form will display a unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug (Sherry and Matthew, 2003). Advances in the pharmaceutical sciences have shown and significant impact in the increasing of the number of approaches for addressing the issues of low aqueous solubility. These strategies for improving and maximize the dissolution rate include micronisation to produce higher surface area for dissolution, the use of salt forms with enhanced dissolution profiles, solubilisation of drugs in co-solvents and micellar solutions, complexation with Cyclodextrins and the use of lipid systems for the delivery of lipophilic drugs (Blagden and Matas, 2007).

Many compounds of pharmaceutical interest have the ability to exist in more than one crystal structure or crystalline form. The commonest crystal forms are polymorph and solvates, that the different polymorph will have a differential in the internal crystal structure and therefore possess different physicochemical properties (Jacob et al. 2011). The differences of the properties make the crystal polymorph are difficult to control in